Reconsideration of the application in view of the following amendments and remarks is respectfully requested.

## I. AMENDMENT

### A. In the Claims

Please amend the following claims.

B1

5. (Amended) The method of claim 1, wherein the cancer cell is a mammalian cell.

6. (Amended) The method of claim 5, wherein the cancer cell is a human cell.

B2

9. (Amended) The method of claim 1, wherein the cancer cell is selected from a group consisting of a bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestine, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, and uterus cell.

10. (Amended) The method of claim 9, wherein the cancer cell expresses PPAR-γ.

B3

13. (Amended) The method of claim 11, wherein the cancer cell is a precursor to osteosarcoma.

B4 sub E1

27. (Amended) The method of claim 1, wherein the thiazolidinedione compound is contacted with the cancer cell at the same time as contact with the chemotherapeutic agent.

31. (Amended) The method of claim 30, wherein the thiazolidinedione compound is contacted with the cancer cell at the same time as irradiation.

B5

32. (Amended) The method of claim 25, further comprising contacting the cancer cell with a therapeutic polynucleotide selected from the group consisting of a Dp gene, p21, p16, p27, E2F, Rb, APC, DC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, *ras*, *myc*, *neu*,

*raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl*, *abl*, Bax, Bcl-X-$_S$ and E1A; wherein the therapeutic polynucleotide is expressed in the cancer cell.

B5 cont.

33. (Amended) A method for treating cancer in a patient comprising administering to the patient troglitazone and a chemotherapeutic drug in an amount effective to produce a therapeutic benefit.

## II. RESPONSE TO OFFICE ACTION

### A. Status of the Claims

Claims 1-46 were rejected by the Office Action. Claim 32 stands rejected under 35 U.S.C. § 112, first paragraph. Claims 5, 6, 9, 10, 13, 27, and 31-33 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 1-8, 16-23, 28, 30, 33-35 and 40-41 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Urban et al. (U.S. Patent No. 5,814,647) as evidenced by Medenica et al. (U.S. Patent No. 5,736,129), Knight et al. (U.S. Patent No. 6,090,407) and Roth et al. (U.S. Patent No. 5,747,469). Claims 1-31 and 33-46 stand rejected under 35 U.S.C. § 103(a) as being obvious over Tontonoz et al. (Proc. Natl. Acad. Sci. 94:237-241) in view of Urban et al. (U.S. Patent No. 5,814,647), Medenica et al. (U.S. Patent No. 5,736,129), Knight et al. (U.S. Patent No. 6,090,407), and Roth et al. (U.S. Patent No. 5,747,469). The specific grounds for rejection, and the Applicants' response thereto, are set out in detail below.

Herein claims 5, 6, 9, 10, 13, 27, and 31-33 are amended. A copy of the claim amendments can be found in Appendix A. Thus, claims 1-46 are the currently pending. A copy of the pending claims is included as Appendix B for the examiner's convenience.

**B. Rejection under 35 U.S.C. § 112, second paragraph**

The Action rejected claims 5, 6, 9, 10, 13, 27, and 31-33 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. As recommended in the Action, Applicants have amended claims 5, 6, 9, 10, 13, 27, 31, and 32 to recite "the cancer cell." Claim 33 has been amended to recite "produce a therapeutic benefit." Support for this amendment can be found in the specification at page 19, line 28 through page 20, line 4. Reconsideration and withdrawal of the rejection is respectfully requested.

**C. Claim 32 is Enabled under 35 U.S.C. § 112, first paragraph**

The Action rejected claim 32 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Action states that the claim encompasses gene therapy for the treatment of cancer *in vivo*, and due to the unpredictability in the art, it would require undue experimentation to practice the invention. Applicants respectfully traverse this rejection.

Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984). "The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)). The claimed invention encompasses contacting the cancer cell with a therapeutic polynucleotide, wherein the therapeutic polynucleotide is expressed in the cancer cell. Methods of contacting a cell with a polynucleotide such that the polynucleotide is expressed in the cell were well known in the art at the time of the present invention. Furthermore, proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana*, 51 F.3d 1560 (Fed.

Cir. 1995). *See also Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark (PTO) proceedings.").

The Action cites Dang, *Clin. Cancer Res.*, 5:471-474 (1999) (hereinafter Dang), for the proposition that the field of gene therapy will need further advancement to make it a reality. The Action lists several factors identified by Dang that are known to limit the effectiveness of gene therapy including: the lack of optimal vectors, the lack of stable *in vivo* transgene expression, the adverse host immune response, and the lack of efficient gene delivery to target tissues. Applicants respectfully point out, however, that Dang focuses on more clinical issues, which are above and beyond the standards for patentability. *See In re Krimmel*, 292 F.2d 948, 954 (C.C.P.A. 1961) ( "There is nothing in the patent statute or any other statutes . . .which gives the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming, and which he has stated are useful for 'pharmaceutical applications,' are safe, effective, and reliable for use with humans.").

Although some obstacles have been encountered in certain gene therapy applications, there have also been many successes in the field. For example, Dang reports that there are approximately 300 approved gene therapy trials (page 471, first paragraph). In addition, Dang discusses studies using HIV-based vectors that have shown "no evidence of brisk immune responses" to the vectors (paragraph bridging page 471 and 472). Even in studies where the host developed an immune response to the vector, the transgene was still expressed (Dang, page 473, paragraph bridging column 1 and 2). Furthermore, clinical trail data suggest that E1A-liposome gene therapy is a feasible cancer treatment (Dang, page 474, column 1, first full paragraph).

The Action also cites Eck & Wilson, *Gene-based Therapy* (1996) (hereinafter Eck) for additional factors that may influence the effects sought to be achieved through gene therapy. The Action specifically identifies the unpredictability in levels of transgene expression, the duration of the expression, and the *in vivo* therapeutic effects. Again, Eck addresses the clinical effectiveness of gene therapy as a whole. It is important, however, to recognize the differences between using gene therapy to treat cancer as compared to inherited disorders. As Eck points out, gene therapy for acquired disorders, such as cancer, is mechanistically more flexible than gene therapy for inherited disorders (page 78, column 2, last partial paragraph). For example, the duration of expression of the transgene in cancer therapy is less of an issue than it is for inherited disorders. In fact, in the treatment of a malignancy, the long-term expression of the therapeutic protein could potentially have deleterious consequences (Eck, page 82, column 1, first full paragraph).

Eck actually re-enforces the Applicants' assertion that methods of delivering therapeutic polynucleotides to cells were well known in the art at the time the invention was made. Numerous DNA delivery strategies are described in the article including viral vectors such as retrovirus, adenovirus, adeno-associated virus, and herpes simplex virus-1 (Eck, page 83-89). Several nonviral delivery strategies are also discussed, including liposomes, uncomplexed DNA, DNA-coated gold particles, and DNA-protein conjugates (Eck, page 90-92). Likewise, the other articles cited in the Action, Miller & Vile, *FASEB*, 9:190-99 (1995); Deonarian, *Exp. Opin. Ther. Patents*, 8:53-69 (1998); and Verma & Somia, *Nature*, 389:239-242 (1997), also describe numerous methods for the transfer and expression of polynucleotides. Applicants contend that the level of skill in the art at the time of the present invention was such that the guidance

provided in the present disclosure would enable one skilled in the art to make and use the claimed invention.

Accordingly, for the above reasons, Applicants contend that the claims are enabled and respectfully request that the rejection be withdrawn.

**D. The Claims Are Not Anticipated by the Cited References**

The Action rejected claims 1-8, 16-23, 28, 30, 33-35 and 40-41 under 35 U.S.C. § 102(e) as being anticipated by Urban *et al.* (U.S. Patent No. 5,814,647) ("Urban") as evidenced by Medenica *et al.* (U.S. Patent No. 5,736,129) ("Medenica"), Knight *et al.* (U.S. Patent No. 6,090,407) ("Knight") and Roth *et al.* (U.S. Patent No. 5,747,469) ("Roth"). The Action states that Urban teaches that troglitazone and related thiazolidinedione compounds can be used in the treatment of climacteric and cancer. It also states that Urban suggests the use of troglitazone therapy in conjunction with chemotherapeutic agents, radiation, or surgery. Although Urban does not teach specifically the chemotherapeutic drugs or types of radiation used, the Action argues that the types of chemotherapeutic drugs and the types of radiation used in the treatment of cancer are well known in the art as evidenced by Medenica, Knight, and Roth. Applicants respectfully traverse this rejection.

The Applicants' invention is directed towards a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound and contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with x-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell. Prior to the Applicants' disclosure it was not known whether the use of thiazolidinedione therapy in combination with other chemotherapeutic agents or radiation would inhibit the growth of a cancer cell. For a prior art disclosure to anticipate an applicant's

invention, the reference must contain an "enabling disclosure." MPEP §2121.01 (quoting *In re Hoeksema*, 399 F.2d 269, 158 U.S.P.Q. 596 (C.C.P.A. 1968)). The amount of guidance needed to enable the invention is inversely related to the predictability in the art. MPEP §2164.03 (citing *In re Fischer*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970)). Biotechnology is a highly unpredictable art. The disclosure by Urban of the use of troglitazone in combination with chemotherapeutic drugs or radiation was not based on actual experiments; it was merely a prophetic example. Due to the lack of predictability in the art, such a disclosure would not enable one of ordinary skill in the art to make and use the invention.

Accordingly, for the above reasons, Applicants contend that the claims are not anticipated and respectfully request that the rejection be withdrawn.

**F. The Claims Are Non-obvious over the Cited References**

The Action rejected claims 1-31 and 33-46 under 35 U.S.C. § 103(a) as being obvious over Tontonoz *et al.* (*Proc. Natl. Acad. Sci.* 94:237-241) ("Tontonoz") in view of Urban *et al.* (U.S. Patent No. 5,814,647), Medenica *et al.* (U.S. Patent No. 5,736,129), Knight *et al.* (U.S. Patent No. 6,090,407), and Roth *et al.* (U.S. Patent No. 5,747,469). The Action alleges that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method disclosed by Tontonoz by combining the use of a thiazolidinedione compound in conjunction with other chemotherapeutic agents to inhibit the growth of liposarcoma cells or mesenchymal tumor cells or tumor cells expressing PPARγ as taught by Urban. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the teaching of the claimed combination and the reasonable expectation of success must both be found in the prior art. MPEP §2143 (citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). The presently cited

references do not teach or suggest that the references be combined. Tontonoz, in fact, teaches *away* from combining thiazolidinedione therapy with chemotherapeutic drugs or radiation by recommending the use of thiazolidinedione compounds as an alternative to conventional chemotherapy (Tontonoz, p. 241, second full paragraph). Urban is said to disclose the use of troglitazone therapy in conjunction with other chemotherapeutic agents or radiation; however, Urban does not teach the use of any specific chemotherapeutic drugs or types of radiation.

Moreover, the disclosed use of troglitazone in combination with chemotherapeutic drugs or radiation was not based on actual experiments. Due to the lack of predictability in the art, such a disclosure would not provide a reasonable expectation of success. As discussed in the argument against the anticipation rejection, the Urban reference is not enabled for a "method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound and contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with x-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell." Furthermore, none of the other references remedies this defect. Therefore, there is no reasonable expectation of success at practicing the claimed invention. Accordingly, there is no *prima facie* case of obviousness.

At most, the references disclose that one skilled in the art might find it "obvious-to-try" the claimed invention. An "obvious-to-try" situation exists when a general disclosure piques the scientist's curiosity, "such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990). The Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C.